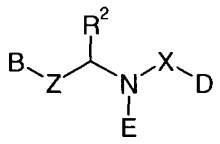
CLAIMS

1. A compound of the general formula (I):

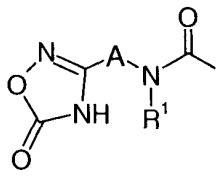


(I)

wherein

R^2 is hydrogen or C_{1-6}-alkyl,

B is



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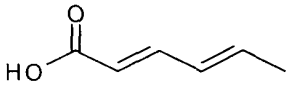

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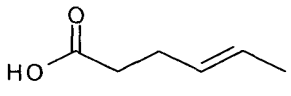
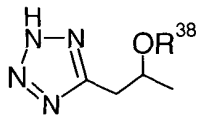


or



,

R^{38} is hydrogen, $-S(=O)_2-C_{1-6}$-alkyl or $-C(=O)-C_{1-6}$-alkyl,

A is a valence bond, $-(CR^3R^4)-$, or $-(CR^3R^4)(CR^5R^6)-$,

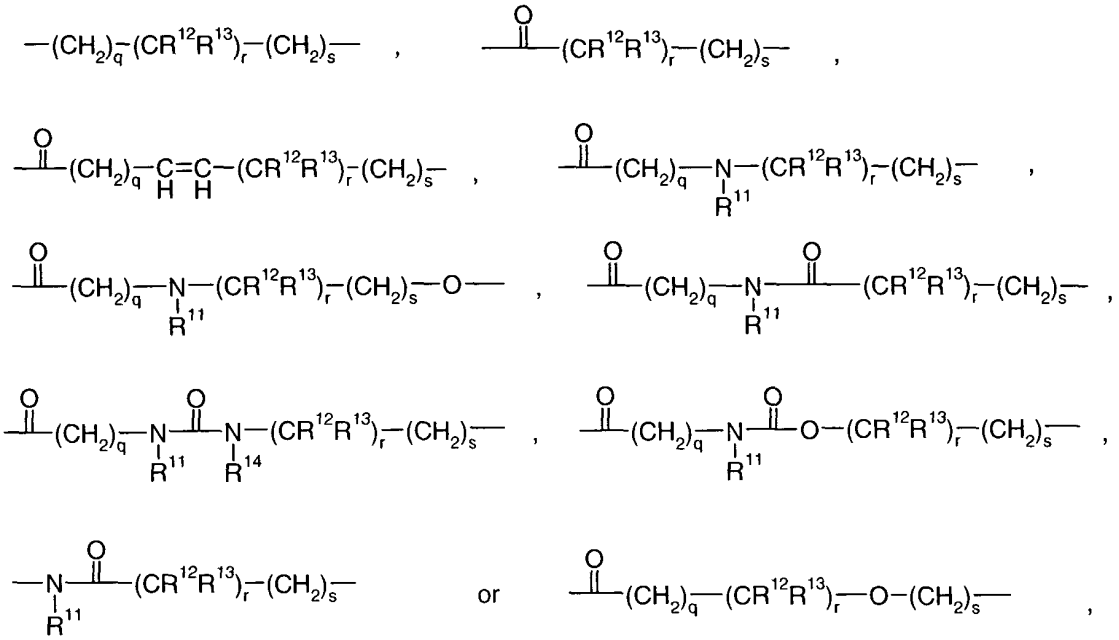
R^1, R^3, R^4, R^5 and R^6 independently are hydrogen or C_{1-6}-alkyl,

Z is arylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^7 and R^8 selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^9$, $-NR^9R^{10}$ and C_{1-6}-alkyl,

wherein R^9 and R^{10} independently are hydrogen or C_{1-6}-alkyl,

X is



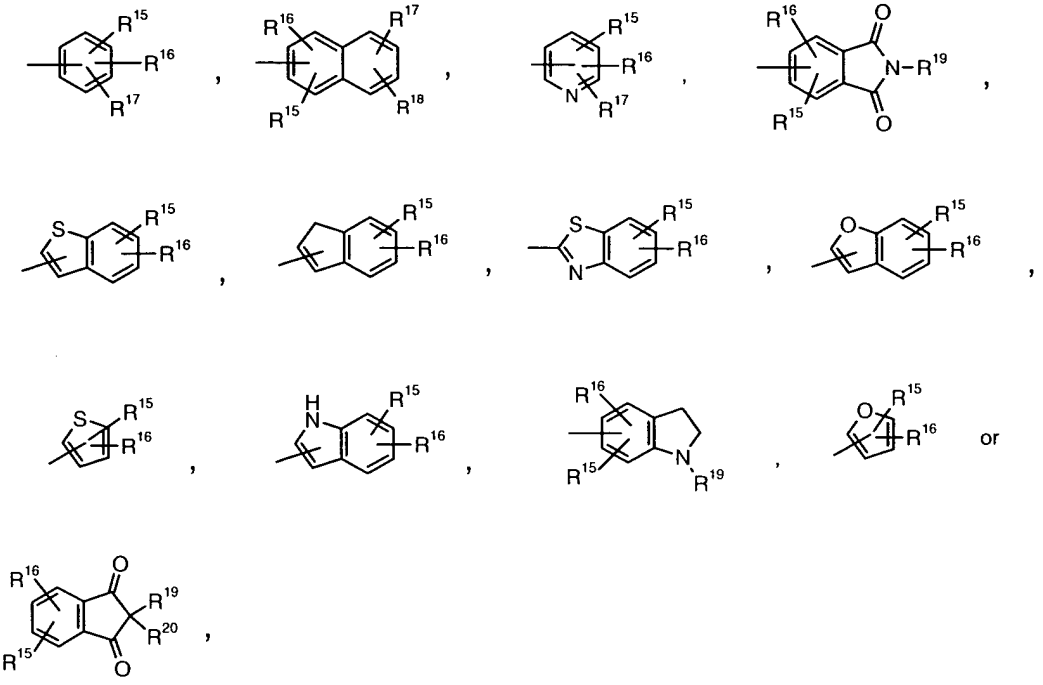
wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{11}, R^{12}, R^{13} and R^{14} independently are hydrogen or C_{1-6}-alkyl,

D is



wherein

R^{15}, R^{16}, R^{17} and R^{18} independently are

hydrogen, halogen, -CN, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$, $-SR^{21}$, $-NR^{21}S(O)_2R^{22}$, $-S(O)_2NR^{21}R^{22}$, $-S(O)NR^{21}R^{22}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-C(O)NR^{21}R^{22}$, $-OC(O)NR^{21}R^{22}$, $-NR^{21}C(O)R^{22}$, $-CH_2C(O)NR^{21}R^{22}$, $-OCH_2C(O)NR^{21}R^{22}$, $-CH_2OR^{21}$, $-CH_2NR^{21}R^{22}$, $-OC(O)R^{21}$, $-C(O)R^{21}$ or $-C(O)OR^{21}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio,

C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{21}$, $-NR^{21}R^{22}$ and C_{1-6}-alkyl,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{21} and R^{22} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{15} to R^{18} when placed in adjacent positions together may form a bridge $-(CR^{23}R^{24})_a-O-(CR^{25}R^{26})_c-O-$,

wherein

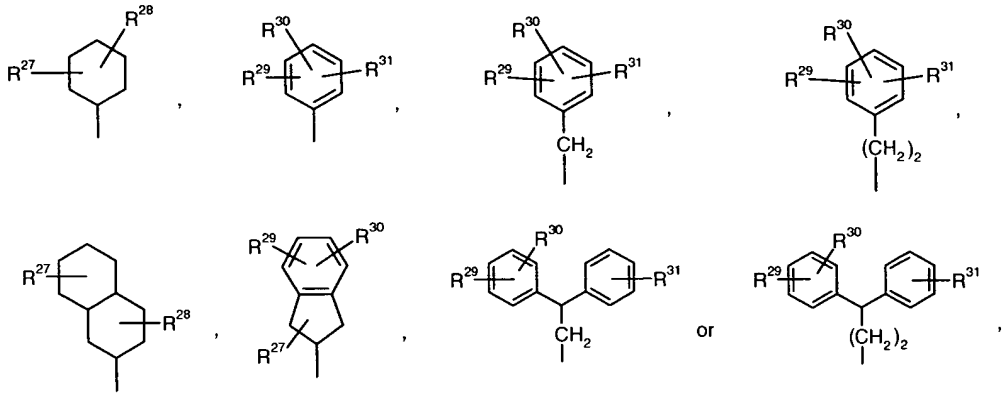
a is 0, 1 or 2,

c is 1 or 2,

R^{23}, R^{24}, R^{25} and R^{26} independently are hydrogen, C_{1-6}-alkyl or fluorine,

R^{19} and R^{20} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is



wherein

R^{27} and R^{28} independently are

hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{32}$, $-NR^{32}R^{33}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl or aryl,

wherein the aryl group optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{32}$, $-NR^{32}R^{33}$ and C_{1-6}-alkyl,

wherein

R^{32} and R^{33} independently are hydrogen or C_{1-6}-alkyl, or

R^{32} and R^{33} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R^{29}, R^{30} and R^{31} independently are

hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{34}$, $-NR^{34}R^{35}$, $-SR^{34}$, $-S(O)R^{34}$, $-S(O)_2R^{34}$, $-C(O)NR^{34}R^{35}$, $-OC(O)NR^{34}R^{35}$, $-NR^{34}C(O)R^{35}$, $-OCH_2C(O)NR^{34}R^{35}$, $-C(O)R^{34}$ or $-C(O)OR^{34}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl, heterocyclyl-C_{2-6}-alkynyl, aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{29}, R^{30} and R^{31} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical $-O-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-O-$, $-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-$ or $-S-(CH_2)_t-CR^{36}R^{37}-(CH_2)_l-S-$,

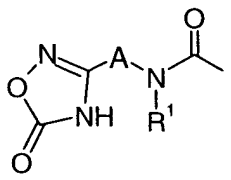
wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{36} and R^{37} independently are hydrogen or C_{1-6}-alkyl,

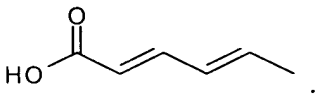
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein B is

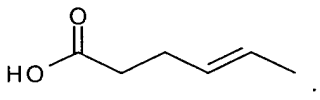


wherein A and R^1 are as defined in claim 1.

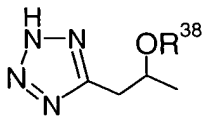
3. A compound according to claim 1, wherein B is



4. A compound according to claim 1, wherein B is



5. A compound according to claim 1, wherein B is



wherein R^{38} is as defined in claim 1.

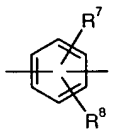
6. A compound according to claim 1, wherein R^1 is hydrogen.

7. A compound according to claim 1, wherein A is a valence bond, $-CH_2-$ or $-CH_2CH_2-$.

8. A compound according to claim 7, wherein A is $-CH_2-$.

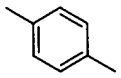
9. A compound according to claim 1 wherein R^2 is hydrogen.

10. A compound according to claim 1, wherein Z is

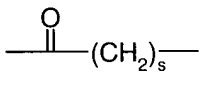
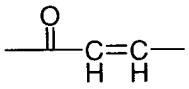
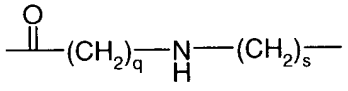


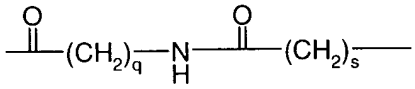
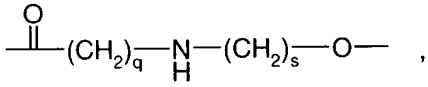
wherein R^7 and R^8 are as defined in claim 1.

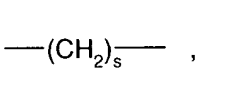
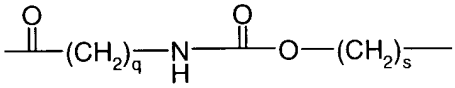
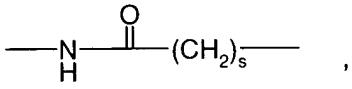
11. A compound according to claim 10, wherein Z is

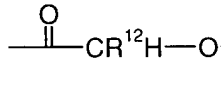
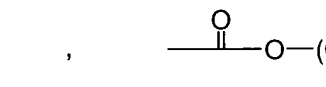


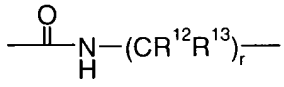
12. A compound according to claim 1, wherein X is

 ,  ,  ,

 ,  ,

 ,  ,  ,

 ,  or



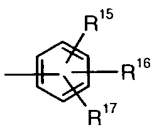
wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R^{12} and R^{13} independently are hydrogen or C_{1-6}-alkyl.

13. A compound according to claim 12, wherein X is -C(O)NH-, -C(O)NHCH$_2$-, -C(O)NHCH(CH$_3$)-, -C(O)NHCH$_2$CH$_2$-, -C(O)CH$_2$-, -C(O)CH=CH-, -(CH$_2$)$_s$-, -C(O)-, -C(O)O- or -NHC(O)-, wherein s is 0 or 1.

14. A compound according to claim 13, wherein X is -C(O)NH-, -C(O)NHCH$_2$-, -C(O)NHCH(CH$_3$)-, -C(O)NHCH$_2$CH$_2$-, -C(O)CH$_2$-, -CH$_2$-, -C(O)- or -NHC(O)-.

15. A compound according to claim 14, wherein X is -C(O)NH-.

16. A compound according to claim 1, wherein D is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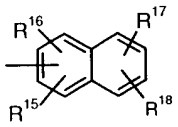
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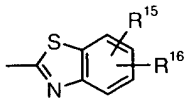
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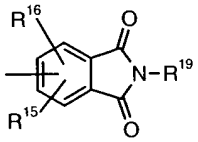
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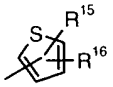
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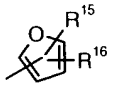
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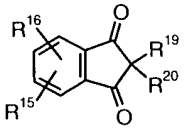
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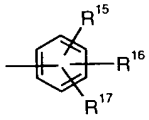
wherein R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} are as defined in claim 1.

17. A compound according to claim 16, wherein D is



wherein R^{15}, R^{16} and R^{17} are as defined in claim 1.

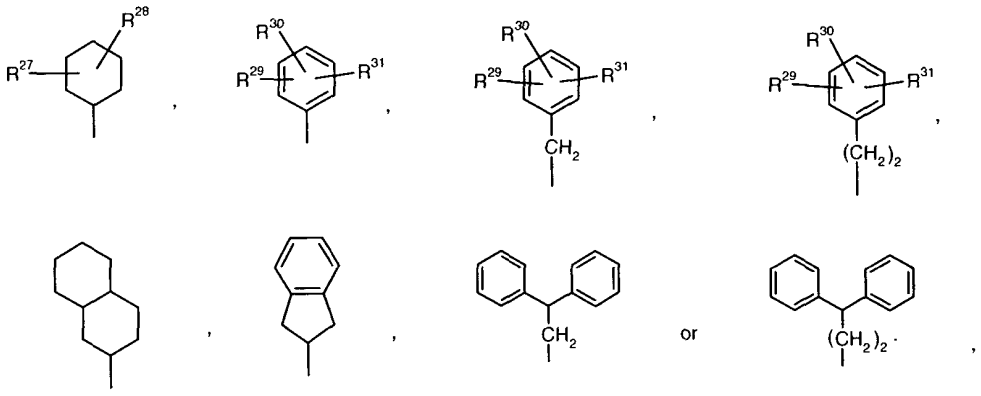
18. A compound according to claim 16, wherein R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, -CN, -NO$_2$, -CF$_3$, -OCF$_3$, -SCF$_3$, C_{1-6}-alkyl, C_{1-6}-alkoxy, -S-C_{1-6}-alkyl, -C(O)OR^{21}, -C(O)R^{21}, -CH$_2$OR^{21}, -C(O)N$R^{21}R^{22}$, -S(O)$_2R^{21}$, -S(O)$_2$CF$_3$, -S(O)$_2$N$R^{21}R^{22}$, C_{3-8}-cycloalkyl or

aryl, or two of the groups R^{15}, R^{16} and R^{17} when placed in adjacent positions together form a bridge $-(CR^{23}R^{24})_a-O-(CR^{25}R^{26})_c-O-$, wherein R^{21} and R^{22} independently are hydrogen or C_{1-6}-alkyl, and a, c, R^{23}, R^{24}, R^{25} and R^{26} are as defined in claim 1.

19. A compound according to claim 18, wherein R^{15}, R^{16} and R^{17} independently are hydrogen, -S-C_{1-6}-alkyl, halogen, -CN, $-CF_3$, $-OCF_3$ or C_{1-6}-alkoxy, or wherein two of the substituents in adjacent positions form the bridge $-CF_2-O-CF_2-O-$.

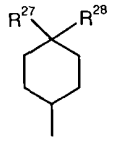
20. A compound according to claim 19, wherein R^{15}, R^{16} and R^{17} independently are hydrogen, halogen, -S-CH_3, $-CF_3$ or $-OCF_3$, or wherein two of the substituents in adjacent positions form the bridge $-CF_2-O-CF_2-O-$.

21. A compound according to claim 1, wherein E is



wherein R^{27}, R^{28}, R^{29}, R^{30} and R^{31} are as defined in claim 1.

22. A compound according to claim 21, wherein E is

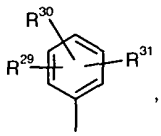


wherein R^{27} and R^{28} are as defined in claim 1.

23. A compound according to claim 21, wherein R^{27} and R^{28} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl or phenyl.

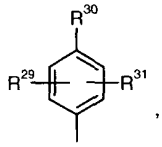
24. A compound according to claim 23, wherein R^{27} is hydrogen and R^{28} is C_{1-6}-alkyl, C_{4-8}-cycloalkenyl or C_{3-8}-cycloalkyl.

25. A compound according to claim 21, wherein E is



wherein R^{29}, R^{30} and R^{31} are as defined in claim 1.

26. A compound according to claim 25, wherein E is



wherein R^{29}, R^{30} and R^{31} are as defined in claim 1.

27. A compound according to claim 25, wherein R^{29}, R^{30} and R^{31} independently are

- hydrogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{34}$, $-NR^{34}R^{35}$, $-SR^{34}$, $-S(O)R^{34}$, $-S(O)_2R^{34}$, $-C(O)NR^{34}R^{35}$, $-OC(O)NR^{34}R^{35}$, $-NR^{34}C(O)R^{35}$, $-OCH_2C(O)NR^{34}R^{35}$, $-C(O)R^{34}$ or $-C(O)OR^{34}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

- C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{34}$, $-NR^{34}R^{35}$ and C_{1-6}-alkyl,

wherein R^{34} and R^{35} independently are hydrogen, C_{1-6}-alkyl or aryl,

or R^{34} and R^{35} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds.

28. A compound according to claim 27, wherein R^{29}, R^{30} and R^{31} independently are

- hydrogen, C_{1-6}-alkoxy, $-CF_3$, $-OCF_3$ or $-NR^{34}R^{35}$, wherein R^{34} and R^{35} are as defined in claim 1, or
- C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, which are optionally substituted as defined in claim 1.

29. A compound according to claim 28, wherein R^{29}, R^{30} and R^{31} independently are

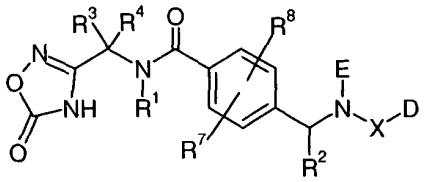
- hydrogen or
- C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl, which are optionally substituted as defined in claim 1.

30. A compound according to claim 29, wherein R^{29}, R^{30} and R^{31} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl.

31. A compound according to claim 30, wherein R^{29} and R^{31} are both hydrogen and R^{30} is C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl.

32. A compound according to claim 31, wherein R^{29} and R^{31} are both hydrogen and R^{30} is C_{1-6}-alkyl.

33. A compound according to claim 1 of the general formula (Ia):

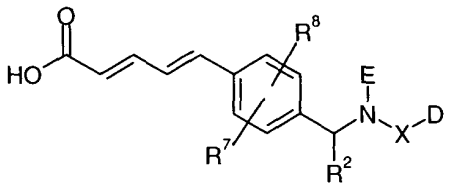


(Ia)

wherein R^1, R^2, R^3, R^4, R^7, R^8, X, D and E are as defined in claim 1 or in any one of the preceding claims.

34. A compound according to claim 33, wherein R^1, R^2, R^3, R^4, R^7 and R^8 are hydrogen.

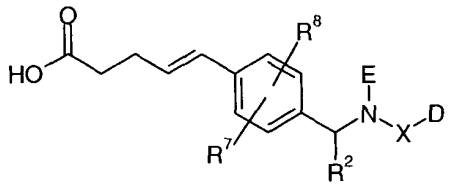
35. A compound according to claim 1 of the general formula (Ib):



(Ib)

wherein R^2, R^7, R^8, X, D and E are as defined in claim 1 or in any one of the preceding claims.

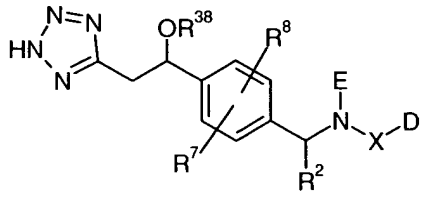
36. A compound according to claim 1 of the general formula (Ic):



(Ic)

wherein R^2, R^7, R^8, X, D and E are as defined in claim 1 or in any one of the preceding claims.

37. A compound according to claim 1 of the general formula (Id):



(Id)

wherein R^2, R^7, R^8, R^{38}, X, D and E are as defined in claim 1 or in any one of the preceding claims.

38. A compound according to claim 35, wherein R^2, R^7 and R^8 are hydrogen.

39. A compound according to claim 1, wherein said compound has an IC_{50} value of no greater than 5 μM as determined by Glucagon Binding Assay (I) or Glucagon Binding Assay (II).

40. A compound according to claim 39, wherein said compound has an IC_{50} value of less than 1 μM as determined by Glucagon Binding Assay (I) or Glucagon Binding Assay (II).

41. A compound according to claim 1, wherein said compound is an agent useful for the treatment and/or prevention of an indication selected from the group consisting of hyperglycemia, impaired glucose tolerance, Type 2 diabetes, Type 1 diabetes and obesity.

42. A compound according to any one of the claims 1 to 41 for use as a medicament.

43. A pharmaceutical composition comprising at least one compound according to claim 1 together with one or more pharmaceutically acceptable carriers or excipients.

44. A pharmaceutical composition according to claim 43 in unit dosage form, said composition comprising from about 0.05 mg to about 1000 mg of the compound according to claim 1.

45. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial.

46. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of glucagon-mediated disorders and diseases.

47. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of hyperglycemia.

48. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for lowering blood glucose in a mammal.

49. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of IGT.

50. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of Type 2 diabetes.

51. Use according to claim 50 for the preparation of a medicament for the delaying or prevention of the progression from IGT to Type 2 diabetes.

52. Use according to claim 50 for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

53. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of Type 1 diabetes.

54. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of obesity.

55. Use according to any one of the claims 45 to 54 in a regimen which comprises treatment with a further antidiabetic agent.

56. Use according to any one of the claims 45 to 55 in a regimen which comprises treatment with a further antiobesity agent.

57. Use according to any one of the claims 45 to 56 in a regimen which additionally comprises treatment with an antihypertensive agent.

58. A method for the treatment or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

59. The method according to claim 58, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg per day.

60. The method according to claim 58, wherein the effective amount of the compound is in the range of from about 0.1 mg to about 1000 mg per day.

61. The method according to claim 58, wherein the effective amount of the compound is in the range of from about 0.5 mg to about 500 mg per day.

62. A method for the treatment or prevention of glucagon-mediated disorders and diseases, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

63. A method for the treatment or prevention of hyperglycemia, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

64. A method for lowering blood glucose in a mammal, said method comprising administering to said mammal in need thereof an effective amount of a compound according to claim 1.

65. A method for the treatment or prevention of impaired glucose tolerance, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

66. A method for the treatment or prevention of Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

67. A method for delaying or preventing the progression from impaired glucose tolerance to Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

68. A method for delaying or preventing the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

69. The method according to claim 58, said method further comprising administering to said subject an antidiabetic agent.

70. The method according to claim 58, said method further comprising administering to said subject an antiobesity agent.

71. The method according to claim 58, said method further comprising administering to said subject an antihypertensive agent.

72. A pharmaceutical composition according to claim 43 in unit dosage form, said composition comprising from about 0.1 mg to about 500 mg of the compound according to claim 1.

73. A pharmaceutical composition according to claim 43 in unit dosage form, said composition comprising from about 0.5 mg to about 200 mg of the compound according to claim 1.

74. A compound according to claim 39, wherein said compound has an IC_{50} value of less than 500 nM as determined by Glucagon Binding Assay (I) or Glucagon Binding Assay (II).

75. A compound according to claim 39, wherein said compound has an IC_{50} value of less than 100 nM as determined by Glucagon Binding Assay (I) or Glucagon Binding Assay (II).